

Optimal design of clinical trials in early stage manifest Huntington's disease

	Early HD (N=123)				Controls (N=123)			
Study dropouts								
	Visit 1	Visit 2	Visit 3	Completed	Visit 1	Visit 2	Visit 3	Completed
	4	6	14	99	6	4	14	99
Follow-up Data Availability								
	Participants with full/partial/no data		Total number of measures		Participants with full/partial/no data		Total number of measures	
SDMT	86/30/7		435		95/21/7		446	
Tapping	89/25/9		426		93/23/7		436	
TMS	94/22/7		445		95/21/7		446	
TFC	94/22/7		445		95/21/7		446	
	Participants with full/partial/no data		Total number of change measures		Participants with full/partial/no data		Total number of change measures	
Brain Volume	67/37/19		261		79/32/12		293	
Caudate Volume	67/37/19		259		76/35/12		286	

Supplementary Table 1: Data availability in Early HD and Control participants.

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		Sample Size Requirements (95% Confidence Interval) according to design and outcome variable									
		SDMT	Speeded Tapping IOI SD	TMS	TFC	Brain Atrophy			Caudate Atrophy		
						mL	%base	%ICV	mL	%base	%ICV
<i>Controls (n)</i>		116	114	-	-	104	104	104	102	102	102
<i>Early HD (n)</i>		116	109	116	116	99	99	99	99	99	99
<u>Design</u>											
Follow-up	Interim visits										
1 year	None	1427 (979, 2270)	2921 (1747, 6358)	3024 (2043, 4920)	2784 (2021, 4764)	664 (476, 1031)	593 (433, 942)	613 (445, 953)	431 (325, 682)	285 (228, 407)	417 (312, 656)
	Six monthly	1426 (978, 2270)	2910 (1741, 6339)	3004 (2032, 4902)	2763 (2003, 4694)	664 (481, 1031)	593 (437, 911)	613 (446, 980)	431 (327, 683)	285 (226, 408)	415 (308, 673)
2 years	None	444 (303, 760)	862 (512, 1992)	945 (688, 1602)	1056 (761, 1761)	295 (222, 470)	268 (206, 418)	269 (203, 434)	149 (112, 258)	99 (82, 143)	156 (117, 256)
	Annual	444 (303, 760)	860 (510, 1988)	939 (683, 1561)	1051 (755, 1761)	295 (224, 488)	268 (208, 417)	269 (206, 432)	149 (113, 256)	99 (82, 142)	155 (117, 256)
	Six monthly	378 (256, 660)	733 (434, 1740)	817 (601, 1384)	947 (680, 1592)	270 (206, 449)	245 (193, 408)	247 (189, 415)	130 (98, 234)	87 (73, 125)	139 (104, 236)
3 years	None	258 (171, 497)	482 (280, 1302)	567 (410, 995)	733 (527, 1238)	227 (166, 391)	207 (155, 353)	206 (151, 357)	97 (69, 187)	65 (51, 99)	107 (76, 195)
	Annual	243 (160, 472)	452 (261, 1245)	537 (389, 954)	707 (506, 1188)	221 (162, 384)	202 (152, 353)	201 (147, 348)	92 (66, 180)	62 (49, 96)	103 (74, 190)
	Six monthly	204 (129, 419)	379 (215, 1101)	469 (329, 866)	646 (460, 1080)	207 (147, 367)	190 (139, 344)	188 (133, 336)	82 (57, 168)	55 (42, 91)	94 (65, 179)
<i>Successful bootstraps (n)</i>		1992	1994	1998	1994	1982	1991	1996	1992	1996	1993

Supplementary Table 2: Predicted sample sizes for clinical trial designs with stratified randomisation and covariate adjustment.

Predicted sample sizes per arm for clinical trials with various outcome variables, assuming the treatment reduces the mean rate of change by 20% (TMS and TFC), and mean excess slope (relative to mean in controls) by 20% (all other outcomes). Sample sizes assume stratified randomisation by (and adjustment for) site only, no dropouts, 90% statistical power and (two-tailed) 5% statistical significance. Bias corrected and accelerated 95% bootstrap confidence limits for sample sizes calculated from 2000 bootstrap samples.

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		Sample Size Requirements (95% Confidence Interval) according to design and outcome variable									
		SDMT	Speeded Tapping IOI SD	TMS	TFC	Brain Atrophy			Caudate Atrophy		
						mL	%base	%ICV	mL	%base	%ICV
<i>Controls (n)</i>		116	114	-	-	104	104	104	102	102	102
<i>Early HD (n)</i>		48	45	48	48	39	39	39	39	39	39
<u>Design</u>											
Follow-up	Interim visits										
1 year	None	1049 (707, 2079)	2397 (1269, 6369)	1616 (1086, 2934)	2342 (1437, 6367)	394 (264, 870)	351 (241, 756)	370 (246, 826)	154 (117, 251)	124 (101, 221)	148 (109, 254)
	Six monthly	1047 (706, 2077)	2388 (1264, 6430)	1600 (1077, 2898)	2304 (1438, 6320)	359 (225, 807)	316 (207, 686)	336 (209, 741)	145 (103, 236)	116 (89, 212)	138 (94, 248)
2 years	None	345 (224, 871)	672 (362, 2004)	543 (423, 936)	871 (528, 2876)	242 (161, 550)	220 (145, 494)	220 (140, 490)	54 (47, 75)	46 (41, 66)	55 (46, 77)
	Annual	344 (225, 870)	670 (360, 1998)	538 (419, 963)	862 (524, 2860)	233 (150, 525)	211 (134, 446)	211 (131, 455)	52 (45, 72)	44 (39, 64)	53 (43, 76)
	Six monthly	299 (192, 791)	565 (304, 1705)	477 (381, 805)	778 (472, 2473)	221 (138, 507)	199 (122, 407)	199 (118, 435)	46 (40, 64)	39 (35, 56)	47 (39, 69)
3 years	None	213 (126, 610)	355 (186, 1236)	353 (262, 585)	598 (350, 2310)	214 (135, 504)	196 (122, 454)	192 (114, 447)	36 (28, 62)	31 (24, 49)	38 (29, 63)
	Annual	202 (118, 583)	331 (171, 1160)	337 (249, 555)	575 (335, 2139)	207 (127, 490)	189 (114, 443)	185 (105, 410)	33 (26, 58)	29 (23, 48)	36 (27, 61)
	Six monthly	176 (94, 510)	270 (137, 1027)	305 (211, 510)	525 (303, 1689)	201 (121, 482)	184 (109, 435)	180 (100, 426)	30 (23, 55)	27 (21, 46)	33 (24, 59)
<i>Successful bootstraps (n)</i>		1976	1949	1989	1993	1986	1997	1997	1996	1995	1998

Supplementary Table 3: Predicted sample sizes per trial arm for CAG enriched clinical trial designs.

Analogous results to those in Supplementary Table 2, but with restriction to CAG > 43 (median).

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		Sample Size Requirements (95% Confidence Interval) according to design and outcome variable									
		SDMT	Speeded Tapping IOI SD	TMS	TFC	Brain Atrophy			Caudate Atrophy		
						mL	%base	%ICV	mL	%base	%ICV
<i>Controls (n)</i>		116	114	-	-	104	104	104	102	102	102
<i>Early HD (n)</i>		58	57	58	58	46	46	46	46	46	46
<u>Design</u>											
Follow-up	Interim visits										
1 year	None	917 (642, 1396)	1780 (1078, 3578)	1749 (1153, 3473)	1506 (1029, 3094)	309 (205, 567)	291 (193, 546)	303 (206, 535)	315 (228, 615)	271 (208, 452)	326 (235, 661)
	Six monthly	916 (642, 1395)	1773 (1075, 3563)	1740 (1145, 3458)	1492 (1016, 3051)	297 (184, 540)	283 (175, 500)	291 (184, 522)	314 (236, 602)	269 (215, 415)	324 (247, 637)
2 years	None	273 (199, 457)	481 (300, 1007)	574 (429, 1081)	580 (362, 1337)	156 (116, 287)	145 (110, 258)	148 (111, 269)	88 (69, 154)	75 (61, 116)	95 (74, 166)
	Annual	273 (199, 456)	479 (299, 1011)	571 (426, 1072)	577 (359, 1337)	153 (112, 282)	143 (108, 255)	145 (107, 265)	88 (70, 151)	75 (63, 104)	95 (75, 160)
	Six monthly	231 (169, 391)	400 (253, 860)	502 (375, 1073)	522 (319, 1207)	144 (108, 273)	135 (104, 242)	136 (102, 257)	72 (59, 113)	60 (52, 84)	78 (62, 128)
3 years	None	152 (109, 293)	244 (154, 543)	361 (260, 652)	407 (239, 1009)	128 (92, 261)	118 (87, 239)	119 (87, 243)	46 (35, 80)	39 (31, 64)	53 (38, 107)
	Annual	143 (102, 345)	225 (142, 512)	344 (244, 625)	393 (229, 959)	124 (90, 257)	115 (86, 234)	116 (85, 239)	42 (33, 74)	35 (28, 57)	49 (35, 103)
	Six monthly	118 (81, 301)	181 (112, 425)	305 (202, 573)	361 (208, 874)	120 (86, 253)	111 (81, 230)	111 (81, 235)	33 (23, 65)	27 (19, 50)	39 (24, 99)
<i>Successful bootstraps (n)</i>		1963	1962	1980	1999	1983	1993	1995	1998	1996	1994

Supplementary Table 4: Predicted sample sizes per trial arm for disease burden enriched clinical trial designs.

Analogous Results to those in Supplementary Table 2, but with restriction to disease burden > 382.2 (median).

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		Sample Size Requirements (95% Confidence Interval) according to design and outcome variable									
		SDMT	Speeded Tapping IOI SD	TMS	TFC	Brain Atrophy			Caudate Atrophy		
						mL	%base	%ICV	mL	%base	%ICV
<i>Controls (n)</i>		116	114	-	-	104	104	104	102	102	102
<i>Early HD (n)</i>		43	39	43	43	48	48	48	48	48	48
<u>Design</u>											
Follow-up	Interim visits										
1 year	None	898 (618, 1539)	1415 (865, 2669)	3862 (2206, 11782)	3481 (1737, 13521)	541 (357, 1022)	472 (308, 843)	491 (323, 917)	337 (244, 598)	249 (194, 469)	341 (242, 628)
	Six monthly	897 (618, 1539)	1412 (864, 2666)	3846 (2199, 11742)	3438 (1697, 13207)	537 (363, 944)	469 (309, 788)	484 (316, 859)	332 (234, 576)	248 (192, 466)	336 (237, 603)
2 years	None	289 (203, 544)	406 (261, 795)	1096 (659, 3439)	1468 (750, 6002)	244 (184, 473)	215 (161, 401)	227 (169, 435)	105 (84, 172)	80 (69, 131)	108 (84, 180)
	Annual	289 (203, 552)	405 (260, 793)	1093 (656, 3434)	1459 (736, 5999)	243 (187, 450)	214 (163, 380)	225 (169, 419)	104 (83, 169)	80 (69, 121)	107 (84, 177)
	Six monthly	248 (173, 490)	342 (220, 676)	919 (549, 3161)	1340 (683, 5429)	226 (175, 396)	199 (152, 355)	210 (159, 389)	90 (75, 145)	70 (61, 95)	93 (75, 147)
3 years	None	174 (116, 381)	219 (135, 500)	574 (345, 2474)	1089 (538, 4401)	189 (137, 372)	168 (120, 322)	179 (126, 368)	62 (49, 104)	49 (39, 73)	65 (49, 115)
	Annual	165 (108, 362)	205 (128, 485)	534 (317, 2251)	1058 (521, 4203)	185 (136, 367)	164 (118, 316)	174 (125, 352)	58 (47, 99)	47 (38, 66)	61 (46, 107)
	Six monthly	140 (87, 325)	168 (102, 458)	428 (248, 1999)	987 (495, 4251)	175 (125, 362)	155 (108, 312)	166 (115, 341)	51 (39, 89)	41 (30, 62)	54 (39, 98)
<i>Successful bootstraps (n)</i>		1973	1936	1929	1979	1990	1997	1996	1996	1996	1996

Supplementary Table 5: Predicted sample sizes per trial arm for clinical stage and baseline brain volume enriched clinical trial designs.

Analogous results to those in Supplementary Table 2, but with restriction to HD2 (clinical) or baseline<74.4%ICV (whole brain) or baseline<0.356%ICV (caudate).

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		Sample Size Requirements (95% Confidence Interval) according to design and outcome variable									
		SDMT	Speeded Tapping IOI SD	TMS	TFC	Brain Atrophy			Caudate Atrophy		
						mL	%base	%ICV	mL	%base	%ICV
<i>Controls (n)</i>		116	114	-	-	104	104	104	102	102	102
<i>Early HD (n)</i>		116	109	116	116	99	99	99	99	99	99
<u>Design</u>											
Follow-up	Interim visits										
1 year	None	1502 (1030, 2390)	3074 (1839, 6693)	3183 (2151, 5179)	2931 (2127, 5014)	781 (560, 1212)	698 (509, 1108)	721 (524, 1121)	507 (382, 803)	335 (269, 478)	490 (367, 771)
	Six monthly	1491 (1022, 2371)	3043 (1820, 6633)	3141 (2122, 5125)	2886 (2092, 4903)	760 (551, 1181)	679 (499, 1045)	702 (510, 1125)	495 (376, 785)	327 (260, 469)	477 (353, 773)
2 years	None	493 (337, 844)	958 (569, 2214)	1050 (764, 1780)	1173 (846, 1956)	394 (296, 627)	357 (274, 557)	359 (271, 578)	198 (149, 344)	132 (110, 190)	207 (156, 341)
	Annual	485 (331, 830)	940 (558, 2173)	1025 (746, 1705)	1144 (821, 1919)	362 (275, 600)	327 (254, 503)	330 (252, 532)	186 (140, 316)	123 (103, 177)	192 (145, 316)
	Six monthly	410 (277, 712)	795 (472, 1891)	884 (651, 1499)	1021 (735, 1715)	327 (251, 530)	296 (235, 493)	299 (230, 487)	160 (121, 285)	107 (90, 154)	170 (127, 289)
3 years	None	344 (228, 662)	642 (373, 1736)	756 (547, 1326)	977 (702, 1651)	349 (255, 601)	319 (238, 543)	316 (232, 550)	148 (107, 287)	99 (79, 151)	165 (117, 300)
	Annual	309 (204, 597)	577 (334, 1574)	682 (494, 1202)	888 (636, 1492)	286 (211, 485)	260 (199, 436)	259 (193, 450)	124 (89, 236)	83 (67, 123)	137 (100, 245)
	Six monthly	244 (155, 495)	456 (258, 1307)	560 (395, 1024)	759 (540, 1275)	261 (190, 452)	239 (180, 413)	237 (174, 408)	107 (75, 215)	72 (56, 114)	122 (86, 226)
<i>Successful bootstraps (n)</i>		1992	1995	1998	1995	1982	1991	1997	1993	1997	1993

Supplementary Table 6: Predicted sample sizes per trial arm for clinical trials taking account of plausible dropout patterns.

Analogous results to those in Supplementary Table 2, but with allowance for dropouts as follows: clinical outcomes: 5% year 1, 5% year 2, 15% year 3; imaging outcomes: 15% year 1, 10% year 2, 10% year 3. No allowance for intermittent missing values.